UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,984	05/08/2008	Jei Man Ryu	027707-00031	2429

4372 7590 10/15/2010

ARENT FOX LLP
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DCIPDocket@arentfox.com
IPMatters@arentfox.com
Patent_Mail@arentfox.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,984	RYU ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a national stage entry of PCT/KR05/03934, filed on 11/22/2005.

Priority

This application claims foreign priority to 10-2004-0096390, filed on 11/23/2004.

Terminal Disclaimer

The terminal disclaimer filed on 8/10/2010 is improper, as it refers to 35 USC § 154, 156 and 173; 35 USC § 155 and 156 do not define the term of the patent. The terminal disclaimer has not been accepted.

Response to Remarks

1. Applicants' arguments, filed on 8/10/2010, with regards to the rejection under 35 USC 103(a) over Suh, in view of Karsenty et. al., and further in view of Allen et. al. have been fully considered but are not found persuasive. The Applicants have argued that the claimed invention would not have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, as Karsenty and Allen teach that structurally different compounds can form di-methanesulfonic acid salts, which are used for the treatment of osteoporosis; therefore, due to the unpredictability in the art regarding the formation of pharmaceutical salts, there would have been no expectation that the di-methanesulfonic salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine would have formed. The examiner respectfully disagrees. Suh et. al. teaches that methanesulfonic acid salts of N-hydroxy-4-{5-[4-(5-

isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine are preferred, and explicitly teaches the mono-methanesulfonic acid salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, for the treatment of osteoporosis. Karsenty et. al. and Allen et. al. teach that the di-mesylate salts of other active agents are preferred over other pharmaceutical salts, as they exhibit good solubility, stability, bioavailability, and are non-hydroscopic. Therefore, as Allen et. al. teaches that the di-mesylate salts have improved solubility, stability, and bioavailability over other salts, one of ordinary skill in the art would have been motivated to prepare the di-mesylate salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, with the expectation of improving solubility, stability, and bioavailability. As it is taught that pharmaceutical salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine can be readily prepared, such as the mono-mesylate salt, and it is taught that the di-mesylate salt of other active agents which have similar utility can also be prepared, one of ordinary skill in the art would have expected success in preparing the di-mesylate salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine. The Applicants have stated that the di-mesylate salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine is unexpectedly superior over the free base and the mono-mesylate salt, regarding solubility and pharmacokinetic properties, and would not have been obvious over the prior art at the time of the invention. While this argument has been fully considered, it is not found persuasive. Allen et. al. teaches that the di-mesylate salt is preferred over other salts, as it has good

solubility, stability, and bioavailability, in comparison to other salts. The di-mesylate salt of the active agent taught by Allen et. al. is also used to treat osteoporosis, and is administered orally; therefore, in consideration of the prior art, it would have been expected that the di-mesylate salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine would have improved solubility and bioavailability over the mono-mesylate salt. As such, the rejection under 35 USC 103(a) over Suh, in view of Karsenty et. al., and further in view of Allen et. al. was proper and is maintained, for reasons of record. For Applicants' convenience, this rejection will be reiterated in the office action. Accordingly, this action is made **FINAL**.

Applicants have traversed the rejection for obviousness type double patenting over the claims of co-pending Application No. 11/577469, and have submitted a terminal disclaimer regarding the rejection. The terminal disclaimer has been disapproved, for reasons discussed supra. Accordingly, this rejection was proper. A modified rejection over the claims of the co-pending application has been made, to account for the cancellation and addition of new claims in the co-pending application. This rejection will be discussed further in the office action.

In response to the rejection for obviousness type double patenting over the claims of US Patent No. 7,662,840, Applicants have argued that as the di-mesylate salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine would have been non-obvious, the instant claims would not have been prima facie obvious over the claims of the US patent. The examiner respectfully disagrees. The claims of the US patent are directed to a method of treating

osteoporosis, comprising administering N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine or a salt thereof to a subject. As the di-mesylate salt is a pharmaceutically acceptable salt, the instant claims and the claims of the US patent are not patentably distinct. This rejection was proper and is maintained, for reasons of record. For Applicants' convenience, this rejection will also be reiterated.

2. Claims 1-9 were examined.

3. Claims 1-9 are rejected.

Claim Rejections-35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

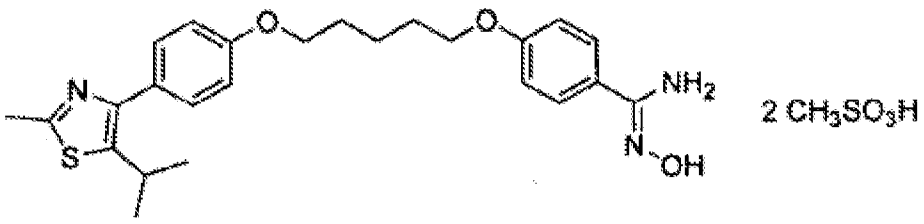
6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh, WO 03/007947 publication, in view of Karsenty et. al., WO 01/53477 publication, and further in view of Allen et. al., US Patent No. 5,914,329 (all of previous record).

The claims are directed to an oral formulation comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt, an inorganic excipient such as calcium carbonate, and a disintegrant such as sodium starch glycolate or sodium croscarmellose.

The structure of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt is shown below:



Suh discloses that the compound, N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, is effective in a composition for treating

osteoporosis (p. 3, lines 23-31). Particularly, Suh teaches pharmaceutically acceptable salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, and that salts of methanesulfonic acid are preferred (p. 4, lines 1-13). Pharmaceutically acceptable carriers comprising the compound and salt forms of the compounds are also disclosed (p.4, lines 19-30), as well as therapeutically effective dosages (p. 5, lines 4-12). As Suh teaches the methanesulfonic acid salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, it would have been expected that in order to form such a salt, the compounds N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine and methanesulfonic acid must undergo a reaction. Suh also teaches that the composition is administered orally (p. 4, line 31-p. 5, line 3).

While Suh teaches that methanesulfonic acid salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine are preferred, the di-methanesulfonic acid salt is not explicitly taught. Suh teaches that excipients are present in the composition (p. 4, lines 25-30); however, excipients such as calcium carbonate and sodium croscarmellose are not explicitly taught.

Karsenty et. al. teaches that the treatment of bone diseases, including osteoporosis, can be accomplished by modulation of neuropeptide Y activity (Abstract; p. 2, middle and last paragraphs). Karsenty et. al. teaches that treatment of conditions associated with decreased bone mass in comparison to non-diseased bone can be accomplished by agents which lower the amount of neuropeptide Y in serum or cerebrospinal fluid or increase the breakdown of neuropeptide Y (p. 3, 2nd paragraph; p.

59, 1st and 2nd paragraphs). It is taught that a variety of different neuropeptide Y receptor antagonists can be used for such treatment, including dimesylate salts (the ionic form of di-methanesulfonic acid) of agents (last paragraph of p. 11-2nd paragraph of p. 12; p. 57, last paragraph-p. 58, top paragraph).

While Karsenty et. al. teaches that dimesylate salts of agents can be used for the treatment of osteoporosis, it is not explicitly taught that the dimesylate salt is preferred or has increased solubility.

Allen et. al. teaches that neuropeptide Y ligands are used to treat a variety of disorders associated with excess neuropeptide Y (Abstract; column 1, lines 8-17). It is taught that the dimesylate salt of the active agent is preferred, as it has good solubility, stability, and good bioavailability in comparison to other salts (column 3, lines 47-58). The dimesylate salt is also non-hydroscopic at a humidity level less than 90 % (column 5, lines 12-13), and can be administered orally (column 6, lines 36-48). Excipients such as calcium carbonate and calcium phosphate are taught to be suitable for tablets, for oral administration (column 6, lines 49-64). While Allen et. al. does not explicitly teach sodium starch glycolate, disintegrants such as various starches and sodium carboxymethylcellulose are taught (column 6, line 64-column 7, line 30). As sodium croscarmellose is sodium carboxymethylcellulose which has been cross-linked, inclusion of such a disintegrant would have been obvious.

One of ordinary skill in the art, at the time of the invention, would have been motivated to prepare the dimesylate (or di-methanesulfonic acid) salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, because Suh

et. al. teaches that the methanesulfonic acid salt is the preferred salt form of this compound which is effective for treating osteoporosis, and Karsenty et. al. and Allen et. al. teach that the dimesylate (di-methanesulfonate or di-methanesulfonic acid) salt of active agents used to treat osteoporosis have better solubility, stability, and bioavailability in comparison to other pharmaceutically acceptable salts. As N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine and the active agents taught by Karsenty et. al. and Allen et. al. are used to treat osteoporosis, and are formulated for oral administration, one of ordinary skill in the art would have expected success in preparing the di-methanesulfonic acid salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, for improved solubility, stability, and bioavailability. Additionally, Allen et. al. teaches that the dimesylate salt is non-hydroscopic up to increased humidity levels. As such, the claims would have been prima facie obvious, as it is taught that the dimesylate salt of active agents used to treat osteoporosis have increased solubility, stability, and bioavailability in comparison to other pharmaceutically acceptable salts.

Claim Rejections-Obviousness Type Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. **Claims 1 and 3-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-20 of copending Application No. 11/577469. This rejection has been modified from the previous rejection presented in the office action dated 4/14/2010, due to the cancellation and addition of new claims in the co-pending application.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to compositions and formulations comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid, and excipients such as calcium carbonate and croscarmellose sodium.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid, and compositions and formulations comprising this compound, along with a carrier and excipients such as calcium carbonate and croscarmellose sodium. The co-pending claims are drawn to an

oral preparation comprising pharmaceutically acceptable salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, as well as excipients such as calcium carbonate and croscarmellose sodium. The co-pending claims are also drawn to ratios of the carbonate to the salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, in an amount from 0.4 to 6 parts by weight to one part by weight, as well as the ratio of the disintegrant to N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine ranging from 0.5 to 5 parts by weight to one part by weight. Tablets, capsules, and granule forms are also included in the co-pending claims. While the instant claims do not explicitly include the weight ratio limitations or the tablet, capsules, or granule forms, such weight ratios would have been obvious in the development of stable formulations, and tablet and capsule forms would have been obvious for oral formulations. Therefore, as both sets of claims are drawn to compositions and oral formulations comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid and excipients, the claims are not patentably distinct from each other.

10. **Claims 1-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-8, 9-11, and 13-15 of U.S. Patent No. 7,662,840.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because while the claims of the instant application are drawn to N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2

methanesulfonic acid and a composition, and the claims of the US Patent are drawn to a method of treatment comprising administration of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine or a pharmaceutically acceptable salt thereof, a method of using a N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid and a composition comprised of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid with excipients would have been prima facie obvious. The US Patent claims are drawn to a method of treatment comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid or a pharmaceutical salt thereof, which would include the di-methanesulfonic acid salt. Additionally a method of making the di-methanesulfonic acid salt and a method of using the salt would also have been prima facie obvious.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

12. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627